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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORRISON & FOERSTER LLP
3811 VALLEY CENTRE DRIVE
SUITE 500
SAN DIEGO, CA 92130-2332

EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	34

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/323,597	Applicant(s) AFAR ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on July 1, 2002 (Paper No. 32) to the restriction requirement of June 9, 2002 has been received. Applicant has elected Group XVII, claims 41, and 48-55 for examination. The election was made with traverse with respect to Group III and without traverse with regard to the remaining groups. Applicants argue (Paper No. 32, page 4) that new Claims 83 and 84 correspond to the claims of Group III in that modulation "by inhibition of growth" or "inhibiting survival or viability" does not constitute a separate invention. This argument has been considered and is found persuasive.

Claims 2-5, and 32-71 were cancelled.

Claims 72-84 are pending and are currently under consideration.

Specification

The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (i.e. see page 23, line 26; page 30, line 35). Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

The specification is further objected to on page 30, line 17 for improper disclosure of nucleotide sequences without a respective SEQ ID No:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825 (see attached Notice to Comply at the end

of this Action). This definition sets forth limits, in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. (see MPEP 2422).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 72-82 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements and or steps, such omission amounting to a gap between the elements or steps. See MPEP § 2172.01. There appears to be an essential feature or step missing from the claimed method in that there is no feature which correlates modulating the cancer cells with assessing the status of cancer cells. How does the modulation effect the status? What is the measured outcome? Is cellular transcription increased? Decreased? Is the modulation indicative of a certain prognostic outcome? Do the cancer cells undergo apoptosis? Cell death? As written, the claims do not clearly point out a relationship between the modulating step and assessing the status of cancer cells which express 20P1F12/TMPRSS2.

Claims 72-82 are further rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a method for "modulating the status" of cancer cells that express 20P1F12/TMPRSS2 has no clear support in

the specification and the claims as originally filed. Applicants argue (Paper No. 26, page 8) that the new claims find support on page 11, line 35 to page 12, line 3; page 15, lines 20-23; and page 18, lines 4-14. However, a review of these passages only appears to provide support for methods of probing or amplifying 20P1F12/TMPRSS2 gene expression, diagnosis and or prognosis of prostate and colon cancer; applications of the 20P1F12/TMPRSS2 polynucleotides capable of directing the expression of 20P1F12/TMPRSS2 polypeptide; tools for modulating or inhibiting the expression of the 20P1F12/TMPRSS2 gene and or translation of the 20P1F12/TMPRSS2 transcript; and as therapeutic agents. The passages further find support for 20P1F12/TMPRSS2 antibodies used therapeutically to modulate or inhibit the biological activity of a 20P1F12/TMPRSS2 protein or targeting and destroying prostate cancer cells expressing 20P1F12/TMPRSS2 protein. Hence, the specification does not appear to provide literal support for the claims drawn strictly to a method of modulating the "status" of a cancer cell. While there does appear to be support for methods of modulating the status of such cancer cells wherein said status comprises "inhibiting growth of the cancer cells" (Claim 83) or wherein said status comprises "inhibiting survival or viability of the cancer cells" (Claim 84), it appears that the subject matter claimed in claims 72-82 broadens the scope of the invention as originally disclosed in the specification.

Furthermore, Claims 72-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a 20P1F12/TMPRSS2 polypeptide and therefore the written description is

not commensurate in scope with the claims drawn to other polypeptides which are related to 20P1F12/TMPRSS2, i.e. "a 20P1F12/TMPRSS2-related protein" or allelic variants.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

What are allelic variants? Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined, nor in this case, is the structure of allelic variant proteins encoded by allelic variant genes defined. With the exception of the 20P1F12/TMPRSS2 polypeptide, the skilled artisan cannot envision the detailed structure of the encompassed variant polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The amino acid sequence itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai*

Pharmaceutical Co. Lts., 18 USPQ2d 1016. Although these court findings are drawn to DNA art, the findings are clearly applicable to the claimed proteins.

Furthermore, although drawn specifically drawn to the DNA art the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly applicable to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". However, there is no disclosure, beyond that of the 20P1F12/TMPRSS2 polypeptide, which meets the description of a genus of polypeptides or 20P1F12/TMPRSS2-related polypeptides.

Therefore, only a 20P1F12/TMPRSS2 protein, but not 20P1F12/TMPRSS2-related proteins meets the written description provision of 35 USC 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Claims 72-84 are broadly drawn to a method of modulating the status of cancer cells that express 20P1F12/TMPRSS2 comprising administering an antibody or fragment thereof or alternatively, administering a recombinant protein comprising the antigen-binding region of an antibody that specifically binds to a 20P1F12/TMPRSS2-related protein, or administering a recombinant polynucleotide the encodes the antibody or fragment thereof in a human mammal wherein modulating the status of the cancer cells comprises inhibiting the growth, survival, or viability of the cancer cells.

The specification teaches (page 17, lines 33-38) that the 20P1F12/TMPRSS2 protein is a cell surface serine protease that may be involved in invasion and metastasis of prostate and colon cancer and that its whole extracellular domain may be a potential therapeutic antibody target. Thus, a reasonable interpretation of the claimed invention is one that reads on a method of

treating cancer in a human mammal wherein said cancer expresses 20P1F12/TMPRSS2. For example, the specification teaches (page 12, lines 5-12; page 13, lines 9-15; page 15, lines 20-23) that antibodies and fragments thereof capable of binding to 20P1F12/TMPRSS2 are useful as cancer vaccines. The specification further teaches (page 18, lines 4-15) that in one approach anti-20P1F12/TMPRSS2 antibodies may be used to treat prostate and colon cancer by introducing into a patient unconjugated antibodies that bind to 20P1F12/TMPRSS2 on prostate or colon cancer cells and mediates the destruction of the cells and the tumor. The therapeutic mechanism of action may include complement-mediated cytolysis, antibody-dependent cellular cytotoxicity, altering the physiological function of 20P1F12/TMPRSS2 and or the inhibition of ligand binding or signal transduction pathways.

However, the specification provides insufficient guidance and objective evidence to enable one of skill in the art to practice the invention (i.e. treating cancer) with any predictability. First, there is insufficient evidence to enable one of skill in the art to reasonably conclude that antibodies or fragments thereof (or polypeptide-like antibodies) would selectively target cancer cells that expressed 20P1F12/TMPRSS2. Those of skill in the art recognize that for an antigen to be considered tumor specific there must be some type of correlative support that differentiates the expression of the antigen in tumor cells versus their normal counterparts. For example, it is well known in the art that that the HER-2/neu oncogene (c-erB-2) is amplified and overexpressed in a variety of human malignances including breast and ovarian cancer and successful attempts at directing antibodies to this protein- in order to treat cancer- have been documented (see US Patent No. 5,770,195). However, with regards to 20P1F12/TMPRSS2, the specification fails to quantify a difference between the expression of 20P1F12/TMPRSS2 in tumor cells versus

normal cells. For example, the specification teaches (page 31, line 16) that differential expression analysis by RT-PCR showed that the 20P1F12 gene is expressed at approximately *equal* levels in normal prostate and the prostate cancer xenografts. Also, Northern expression analysis indicated similar expression *levels* in the prostate cancer xenografts and normal tissues (page 32, lines 1-3; also Figure 7). As evidenced by Weiner (Seminars in Oncology, Vol. 26, No.4, 1999, pages 41-50), one of the major obstacles to successful monoclonal antibody therapy is antigenic heterogeneity and insufficient target specificity (Table 2, page 42). Weiner teaches that heterogeneity of antigen expression by tumor cells restricts the percentages of cells that can be reliably targeted. This heterogeneity is manifested not only as the presence or absence of antigen on a cell, but also by relative expression of antigen on a given cell. An additional obstacle relates to the relative scarcity of tumor-specific antigens that may be targeted by antibody-based molecules (page 43, 2nd column, 2nd paragraph). Thus, one of skill in the art, upon reading the disclosure, would not reasonably predict that the claimed method would selectively and specifically inhibit the growth of cancer cells expressing 20P1F12/TMPRSS2 as there is insufficient guidance and objective evidence that 20P1F12/TMPRSS2 is overexpressed in cancer cells versus normal cells. Secondly, the specification fails to demonstrate the *in-vitro* or *in-vivo* modulation of any cancer cell which expresses 20P1F12/TMPRSS2 wherein said modulation comprises inhibiting growth, survival, or viability of said cancer by administering to the cancers cells: 1) antibodies or fragments thereof which specifically bind to 20P1F12/TMPRSS2-related polypeptide; 2) polypeptides comprising the antigen-binding region of an antibody that specifically binds to a 20P1F12/TMPRSS2-related protein; or 3) recombinant polynucleotides which encode the antibody or fragment thereof.

In general, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, with regards to peptide immunotherapy, Bellone *et al.* . (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth *in-vivo* (Figure 10, page 1486). All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for one of skill in the art to practice the method with any predictability as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
August 22, 2002